Introduction to Prophylactic Vaccines and Clinical Studies

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August 2022

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Vaccine Classification

Manufacturing process

- Inactivated vaccine
- Live-attenuated vaccine
- SUBUNIT vaccine
- Conjugate vaccine
- VLP Vaccine
- Vector Vaccine
- Nucleic Vaccine

Route of medication

- Injection: intramuscular, intradermal, subcutaneous
- Digestive tract: Oral
- Respiratory tract: nasal spray, inhalation

Type of antigen

- Multi-component vaccine
- Polyvalent vaccine

Vaccine Classification

Class 1: Innovative vaccines: Vaccines that have not been marketed in China and abroad

1.1 Vaccines for diseases without effective prophylaxis.
1.2 New antigen forms developed on the basis of marketed vaccines.
1.3 Vaccines containing new adjuvant or new adjuvant system.
1.4 Multi-component/ multivalent vaccine containing new antigen or new antigen forms.

Class 2: Modified vaccines: Vaccines that are modified from the products marketed both in China and abroad to achieve improvement in safety, effectiveness and quality controllability in the new product and have obvious advantages

2.1 Vaccines with changed antigen profile or type based on products marketed both in China or abroad and with obvious clinical advantages.
2.2 Vaccines with major technological improvement
2.3 New multi-component/multivalent vaccines composed of vaccines with similar products marketed.
2.4 Vaccines with changed administration route and obvious clinical advantages.
2.5 Vaccines with changed immunization dose or procedure and obvious clinical advantages in new dose or procedure.
2.6 Vaccine with changed target population.

Class 3: Vaccines marketed at home or abroad

3.1 Marketing application of vaccines that have been produced and marketed abroad, but not marketed domestically.
3.2 Application for domestic production and marketing of vaccines that have been marketed abroad, but not marketed domestically.
3.3 Vaccines marketed domestically.

Relevant Clinical Evaluation

Take effectiveness as an example

- **Conduct effectiveness evaluation mainly through immunogenicity (mostly seen in Registration Class 3)**
- **Conduct effectiveness evaluation mainly through protection efficacy (mostly seen in Registration Class 1)**
  - **Mainly humoral immunity or as an important component: The detection and evaluation of serum binding or neutralizing antibodies has been relatively mature, and the immune response induced by vaccines can be used to support the evaluation on whether there are differences in product quality attributes**
  - **Mainly cellular immunity: The study is far from sufficient as that of humoral immunity and there are many challenges in the evaluation, such as the lack of consensus on detection time, specific detection indicators (T-cell classification, cytokines), specificity of immune response, and selection of non-inferiority margin. It is difficult to provide further support for the evaluation of CMC change through clinical studies;**
  - **Mainly mucosal immunity: The collection of specimens () for IgA antibody detection is difficult. It is also difficult to provide further support for the evaluation of CMC change through clinical studies**

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- Vaccine Classification and Clinical Evaluation
- CMC Change related Clinical Study

Clinical Evaluation of Inter-Batch Consistency

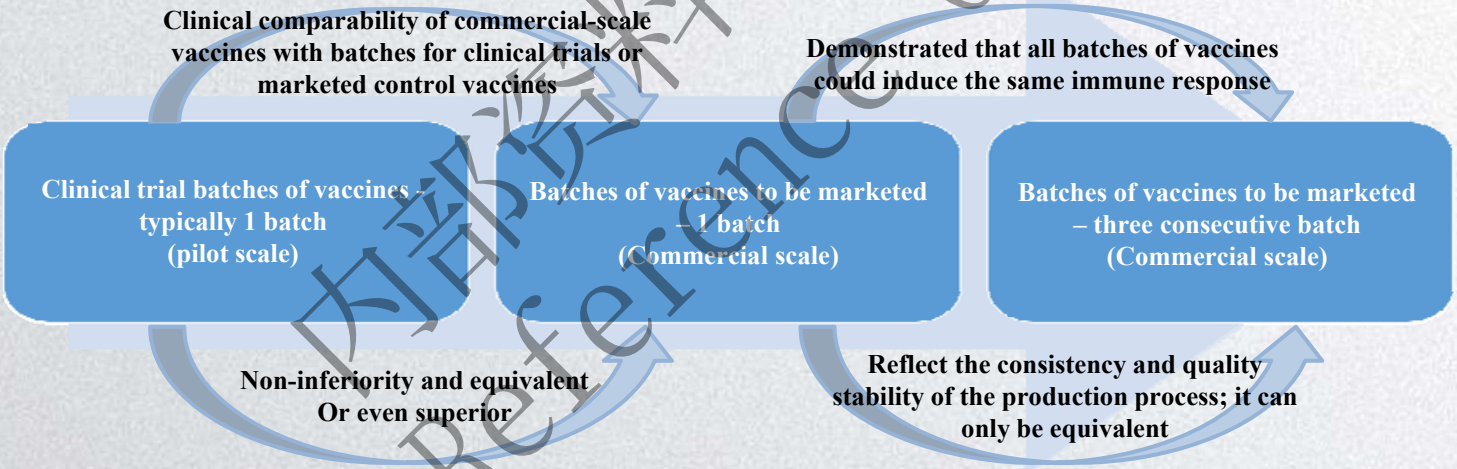
Technical Guidelines for Clinical Comparability of Prophylactic Vaccines

Clinical study of inter-batch consistency, that is, to use commercial scale products to evaluate the quality stability and process repeatability of successive batches of test vaccines through immunogenicity indicators after human immunization, so as to ensure the quality controllability of vaccines registered and marketed.

- **In general, sufficient batches of commercial-scale test vaccines should firstly be used for adequate CMC comparison studies with vaccine batches for clinical trials for the consistency and quality stability of the manufacturing process between batches.**
  - The comparison between commercial scale and clinical trial scale is essentially a scale-up CMC change (pre-marketing)
  - Firstly, the CMC comparison study is carried out, focusing on whether the scale-up products to be commercialized are comparable with the samples for key clinical trials for registration, and the safety and effectiveness results can be referred to
  - Non-clinical and/or clinical study of the product after the change is not required if the production process, quality and stability study of the product before and after the change is sufficient to demonstrate comparability. **However, non-clinical and/or clinical bridging or confirmatory study should be performed when the relationship between specific quality attribute and safety and effectiveness has not been established and differences in quality attributes of the product before and after the change are observed.**

Clinical Evaluation of Inter-Batch Consistency

- **For test vaccines with a high degree of variation in production process or a certain degree of quality difference between the product to be marketed and the clinical samples, clinical comparative study should also be conducted on the consistency of the test vaccines among batches. Clinical study of inter-batch consistency should include at least three consecutive batches of commercial-scale vaccines to demonstrate:**



Clinical Evaluation of Inter-Batch Consistency

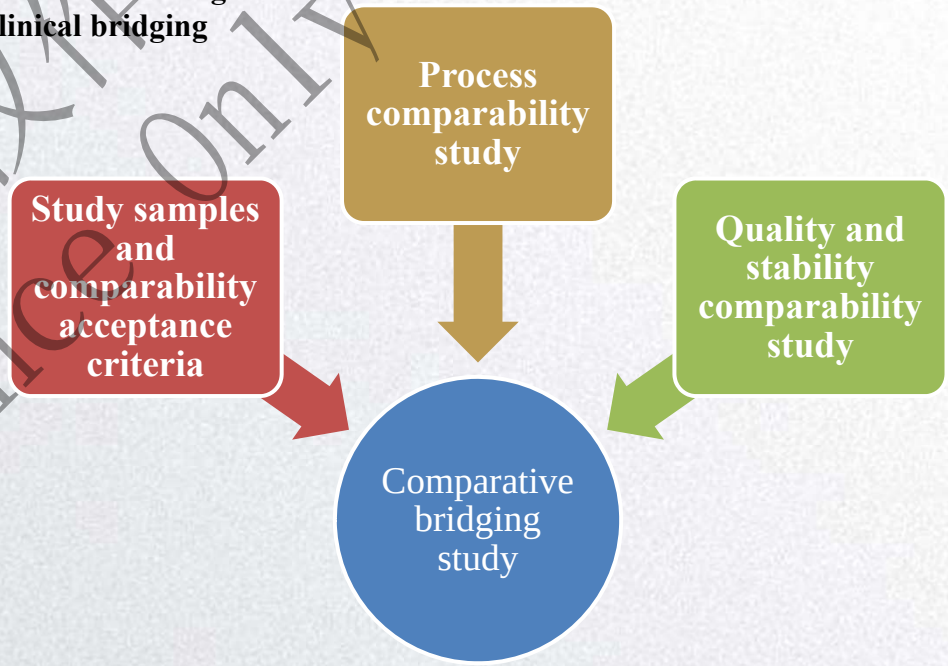
- **The study data of batches for clinical consistency comparison will provide support for the lower limit of the effectiveness and upper limit of safety of the limit of the key test items in the quality specifications (e.g., range of upper and lower limits of antigen content/titer, virus titer, etc.), ensure a scientific and reasonable quality specification, and thus further guarantee the safety, effectiveness and quality controllability of marketed vaccines.**
- **The indicators and criteria for immunogenicity evaluation can be referred to randomized controlled clinical trials.**
  - Only applicable to vaccines that can use serum antibodies to evaluate humoral immunity and thus evaluate the comparability of overall immune response
  - Comparability of commercial-scale vs clinical batches and that of commercial batches are essentially two studies that may have different study assumptions and be conducted separately
  - Even if carried out simultaneously (1 clinical batch and 3 commercial batches), they should be based on their own assumptions and subject to respective analysis: it is not recommended that the 3 commercial batches be merged after equivalence is met for comparison with 1 clinical trial batch.

CMC Change related Clinical Study

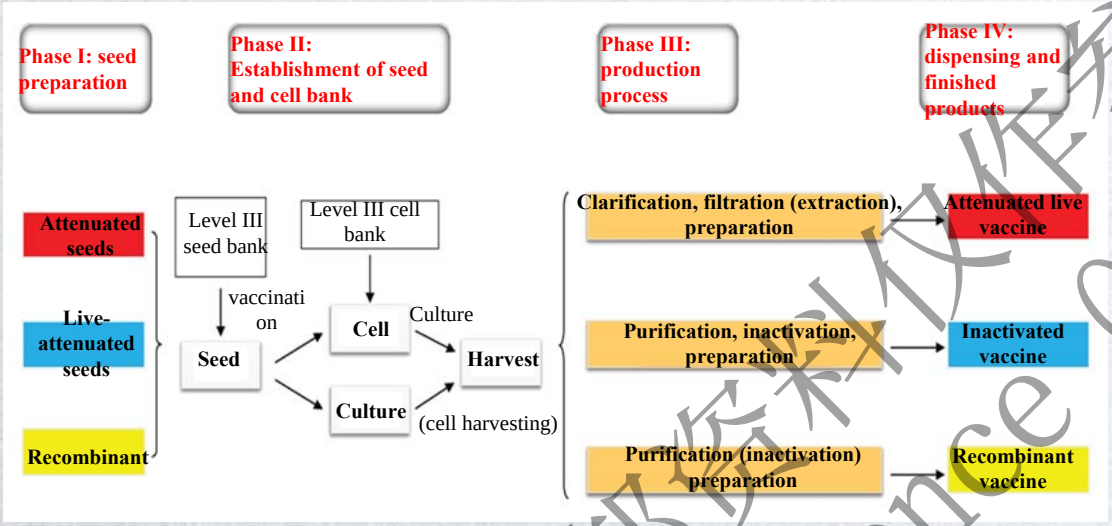
Technical Guidelines for Studies on CMC Changes to Marketed Biological Products (Interim)

Change comparability study is progressive process that, in addition to conducting CMC comparability studies, should include non-clinical or/and clinical bridging study in some cases.

- **If the production process, quality and stability study of the product before and after the change is sufficient to prove the comparability, then non-clinical and/or clinical study on the product after the change is not required.**
- **However, when the relationship between specific quality attributes and safety and effectiveness has not been determined, and the differences in product quality attributes before and after the changes are observed, non-clinical and/or clinical bridging or confirmatory study should be implemented.**



CMC Change related Clinical Study



- Carry out process verification of three consecutive commercial scale batches of bulk and preparations (if there is any impact on the preparations).
- Use at least three batches of the packaging containers proposed for change for stability studies, except for special requirements
- The stability data are from at least three batches of intermediates and bulk of commercial production scale
- Compare the dissolution/release behaviors of the preparations of 3 batches of samples before and after the change.
- Provide process verification data of 3 consecutive batches of adjuvants, quality comparison study data of adjuvant before and after the change, and stability process verification data.
- Carry out release verification for 3 consecutive batches of diluent after the change and carry out a comparability analysis with the historical data before the change.

In order to support major post-marketing CMC changes of biological products, comparability study samples should generally include at least 3 consecutive batches of commercial-scale products after the change.

- **Example: major CMC changes may involve various links of production process**
- **CMC changes should be analyzed based on three batches, and the immunogenic bridging clinical study should have three test groups accordingly**
- **After the previous CMC change study, any batch of the product before the change can be considered to have good representativeness, so there may be one control group set.**

Immunogenic Bridging Study

To begin with the end:

- **The purpose of the study differs from that of a key registration study, for example, the comparability with a control vaccine need not be demonstrated in the entire target population**
- **Focus more on the evaluation of whether the CMC change leads to the change of product quality attributes through human immune response, and whether the safety and effectiveness results and benefit-risk ratio conclusions of the products before the change can be used for reference**
- **In addition to ensuring intergroup equalization in general critical registration studies, interference from non-product factors should be minimized**

Begin with the end to have clear objectives
Conduct scientific design to avoid risks
Strictly perform standardized operation
Conduct sufficient and appropriate data analysis

Risk-benefit assessment

Immunogenic Bridging Study

- **Overall design:** Randomized, double-blind, controlled:
  - Maximize the balance among groups, including known and unknown influencing factors
  - There should be three test groups set, which are vaccinated with three batches of commercial scale/changed vaccines (three consecutive batches) respectively.
  - There may be one control group, which is vaccinated with a batch of clinical pilot scale/pre-change vaccines
  - It can be implemented separately or synchronously

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Risk-benefit assessment

Immunogenic Bridging Study

- **Subject selection:** Further reduce the interference of known factors
  - Impact of previous vaccination/infection history on vaccine immune response
    - ✓ Exclude those with a clear history of previous infection/development and previous vaccination history at the time of enrollment (enrollment testing may be carried out if necessary).
    - ✓ Carry out natural infection prevention and control of the vaccination with similar vaccines in the study period;
    - ✓ Take the baseline antibody negative population (maximized representativeness as no previous vaccination/infection history) was used as the primary evaluation population for the analysis
  - If there are differences in immune responses at different ages, select a narrow age group only (e.g., 18-25 years old).
  - Special populations, such as those with underlying diseases, should be excluded if they have an impact on the immune response
  - Refer to the safety results obtained from clinical trials of test vaccines and adjust the exclusion criteria as necessary

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Immunogenic Bridging Study

Immunogenicity evaluation criteria: Clinical comparability studies of prophylactic vaccines

- **If the antibody positive conversion rate is used as the primary evaluation index, 1/20 to 1/10 of the lower limit of the bilateral 95% confidence interval is generally used as the equivalent/noninferiority margin of the rate difference. If the rate ratio method is adopted, bilateral 95% confidence intervals (equivalences) for the ratio of antibody conversion rate (test vaccine/control vaccine) should be within (0.8,1.25); The lower limit of the unilateral 97.5% confidence interval (noninferiority interval) for the ratio of antibody positive conversion rate (test vaccine/control vaccine) should be no lower than 0.8**
- **If GMT or GMC is used as the primary evaluation index, the lower limit of the bilateral 95% confidence interval (equivalent interval) for the GMT or GMC ratio of the test vaccine/control vaccine should generally be within (0.67,1.5); The lower limit of the unilateral 97.5% confidence interval (noninferiority interval) for the GMT or GMC ratio of the test vaccine/control vaccine should be no lower than 0.67**
  - **If a trial involves more than one primary endpoint (e.g., a clinical trial of a polyvalent vaccine), the trial design should consider whether to make adjustment for Type I statistical errors based on the testing hypothesis. For polyvalent vaccines, the equivalence/noninferiority margin can be moderately relaxed on the basis of conservative principles, and (0.5, 2) may be used.**

Immunogenic Bridging Study

- **Immunogenicity evaluation criteria: Immunogenic bridging of CMC changes**
  - **A pairwise comparison of the immunogenicity of each batch of test vaccines should meet the standard of equivalence, and the difference between batches should be within the clinically acceptable range (equivalent margin)**

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Risk-benefit assessment

  - **Positive conversion rate, protective threshold ratio and other indexes may be easier to reach higher level (for example, rabies vaccine generally achieves 100% positive conversion/protection, and most vaccines can achieve 95% above % positive conversion), and can not fully reflect whether there is any difference in the actual level of immune response, so the immunogenic bridging study of CMC changes generally select antibody levels as the primary evaluation index for the equivalence**
  - **The 95% confidence intervals for the GMT or GMC ratios between batches fall within the range of equivalence margin (1/Δ，Δ) (Δ mainly refers to the maximum detection error allowed by the GMT laboratory). The 95% confidence intervals of GMT or GMC ratios between batches usually select (0.67, 1.5) or (0.5, 2) as equivalence margin according to vaccine characteristics; The basis for the selection of the equivalence margin should be provided**
  - **It is necessary to reasonably select antibody indicators based on the adequacy of the study on vaccine immune response mechanism and the maturity of relevant detection methods. For example, for innovative vaccines, neutralizing antibodies, especially neutralizing antibodies of euvirus, that can more directly reflect the protective effect are generally used for evaluation**

Immunogenic Bridging Study

- **The requirements of quality management should be equivalent to those of clinical trials for vaccine registration. The clinical trial process should be implemented in strict accordance with the GCP requirements to ensure the quality of clinical trials**

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Risk-benefit assessment

- **All laboratory indicators (such as serology, cytology, etiology, etc.) should be tested in accordance with the methods and requirements defined in the clinical trial protocol in testing institutions that have passed the national laboratory accreditation or have laboratory qualification certification**
- **Before and after the change, the vaccines should undergo the retest of antigen content/titer simultaneously, and their periods of validity should be kept comparable as far as possible.**
  - It is not recommended to use backup sera from previous studies of the vaccines of clinical batches/before the change as control group: there may be impact on antibodies after repeated thawing (non-product influencing factors)
  - Blood samples involving the primary endpoint of immunogenicity should be tested simultaneously and in parallel

Immunogenic Bridging Study

- **Although certain safety data have been accumulated for the vaccines of clinical batches/before the change, attention should still be paid to the risk control in the trial to ensure the safety of subjects.**
- **It is encouraged to conduct immunogenicity comparison after each immunization; Immune persistence is also an important part of immunogenic bridging**

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Risk-benefit assessment

- **For the sample size estimation of inter-batch consistency tests, attention should be paid to the decrease of test power caused by Type II error inflation; In addition to immunogenicity, it is also necessary to consider the minimum requirements of whether safety varies before and after the change for sample**
- **The statistical analysis plan should be scientifically developed, the studies (1 clinical batch and 3 commercial batch) should be conducted simultaneously, and analysis should be carried out respectively based on their respective research assumptions**
  - it is not recommended that the 3 commercial batches be merged after equivalence is met for comparison with 1 clinical trial batch.
  - Corresponding guidelines for statistical analysis are being developed